

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effectiveness of implementation interventions in improving physician adherence to guideline recommendations in heart failure: a systematic review
AUTHORS	Shanbhag, Deepti; Graham, Ian; Harlos, Karen; Haynes, R. Brian; Gabizon, Itzhak; Connolly, Stuart; Van Spall, Harriette Gillian Christine

VERSION 1 – REVIEW

REVIEWER	Pierpaolo Pellicori, research fellow Academic Cardiology, Hull and York Medical School, UK
REVIEW RETURNED	28-Jul-2017

GENERAL COMMENTS	<p>In this paper, authors systematically reviewed interventions that improve HF management and outcome. Because of the vast heterogeneity of 35 studies identified (of which only 9 were randomised controlled trials) authors were unable to conduct a meta-analysis and to provide definitive conclusions.</p> <p>I felt that the review is well designed (protocol was registered and already published in a peer-reviewed journal) and conducted. It is well written and authors nicely summarise their findings.</p> <p>I think the work is very comprehensive but whether audit, education or any other intervention might improve implementation of guidelines and outcome, and in whom, remains to be demonstrated.</p> <p>Well done.</p>
-------------------------	---

REVIEWER	Antonio Cittadini Prof. Antonio Cittadini Associate Professor of Medicine Department of Translational Medical Sciences University Federico II Via Pansini 5 80131 Naples ITALY Head of Interdisciplinary Research Centre in Biomedical Materials (CRIB) Piazzale Tecchio, 80 80125 Naples ITALY
REVIEW RETURNED	22-Sep-2017

GENERAL COMMENTS	Shanbhag et al. performed a systematic review regarding the effectiveness of implementation interventions aimed in improving guideline uptake in heart failure.
-------------------------	---

	<p>The paper is well-written, the topic is rather interesting, the used methodology is clear and correct.</p> <p>As acknowledged by the authors, a huge limitation of the work is that the heterogeneity of the published studies does not allow a meta-analysis. This doesn't allow any possible conclusion and makes the paper only a description of available literature.</p> <p>I have some suggestions in order to improve the quality of the manuscript:</p> <ul style="list-style-type: none"> -Throughout the whole manuscript, no mention was done with regards to the presence of studies dealing specifically with Heart failure with preserved ejection fraction. It seems that all studies dwelled upon heart failure with reduced ejection fraction. If this is the case, I would change the title into "Effectiveness of implementation interventions in improving physician adherence to guideline recommendations in heart failure with reduced ejection fraction: a systematic review". Moreover the definition heart failure with reduced ejection fraction (HFREF) should also be used in the manuscript instead of the generic all-encompassing heart failure. -Abstract: The results section of the abstract is quite long and hard to follow. I would suggest to delate the description of the type of study "including 9 randomized controlled trials (RCTs). Provider level interventions (N=13 studies) included: audit and feedback, reminders, and education. Organization-level interventions (N=15) included: medical records systems changes, multidisciplinary teams, and clinical pathways. System-level interventions (N=3) included: provider/institutional incentives. Four studies assessed multi-level interventions." -Abstract: I would add in the conclusion (page 3 lines 14) "However, improvements in process outcomes were rarely accompanied by improvements in clinical outcomes. " -Results: there were studies dealing with the target dose for each kind of medications? How many patients reached the target dose of ACE-I or Beta-blockers or MRA after implementation of interventuison. -The discussion is too long and very hard to follow. Moreover I would be more focused on these aspests: 1) conclusion cannot be drawn from this work 2) which kind of guidelines measures were the most studied (acei? Betablockers? ICD?) 3) the authors should also discuss the importance of reaching the target dose for medications.
--	--

REVIEWER	Ulrich Siering Institute for Quality and Efficiency in Health Care (IQWiG) Department for Health Care and Health Economics Germany
REVIEW RETURNED	18-Oct-2017

GENERAL COMMENTS	<p>Page 4. line 18: There are several more current systematic reviews on guideline implementation. The review of Grimshaw contains only studies published until 1998.</p> <p>More current reviews are listed here (from page 158ff): https://www.iqwig.de/download/V12-04_Abschlussbericht_Umsetzung-von-Leitlinien.pdf</p> <p>Perhaps also interesting: Unverzagt S, Oemler M, Braun K, Klement A. Strategies for guideline implementation in primary care focusing on patients with cardiovascular disease: a systematic review. Fam Pract 2014; 31(3): 247-266</p>
-------------------------	--

	<p>Page 11ff, Table 3: The control interventions should be mentioned - in table 3 and the corresponding text.</p> <p>Page 25, table 4: Table 4 is not helpful. It should be considered to delete the table or to find a different form of presentation.</p> <p>Page 34. line 49 and page 35. line 35: Citation [58] and [60] are the same</p> <p>Page 35. line 16. The statement that audit and feedback are "largely ineffective" is not correct. Die Conclusion of Ivers et al is: "AUTHORS' CONCLUSIONS: Audit and feedback generally leads to small but potentially important improvements in professional practice. The effectiveness of audit and feedback seems to depend on baseline performance and how the feedback is provided. Future studies of audit and feedback should directly compare different ways of providing feedback." Ivers et al should be cited correctly.</p> <p>Page 35, line 27: Citation [64] is the updated version of [65]. I think, it is not necessary to cite [65].</p> <p>Page 36, line 21ff: The authors state, that one of the greatest limitation of their study is the inclusion of studies with "observational and quasi-experimental study design". The authors should explain, why the inclusion of theses studies was necessary.</p> <p>Page 51. fig. 1: The numbers in the flow chart are not correct: Article Screened: 2424, excluded: 2299, Full-text: 126. $2299+126 = 2425$ (not: 2424)</p>
--	---

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Pierpaolo Pellicori, research fellow

Institution and Country: Academic Cardiology, Hull and York Medical School, UK

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

In this paper, authors systematically reviewed interventions that improve HF management and outcome. Because of the vast heterogeneity of 35 studies identified (of which only 9 were randomised controlled trials) authors were unable to conduct a meta-analysis and to provide definitive conclusions.

I felt that the review is well designed (protocol was registered and already published in a peer-reviewed journal) and conducted. It is well written and authors nicely summarise their findings. I think the work is very comprehensive but whether audit, education or any other intervention might improve implementation of guidelines and outcome, and in whom, remains to be demonstrated. Well done.

Reviewer: 2

Reviewer Name: Antonio Cittadini

Institution and Country

Department of Translational Medical Sciences, University Federico II, ITALY

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

Shanbhag et al. performed a systematic review regarding the effectiveness of implementation interventions aimed in improving guideline uptake in heart failure.

The paper is well-written, the topic is rather interesting, the used methodology is clear and correct. As acknowledged by the authors, a huge limitation of the work is that the heterogeneity of the published studies does not allow a meta-analysis. This doesn't allow any possible conclusion and makes the paper only a description of available literature.

I have some suggestions in order to improve the quality of the manuscript:

-Throughout the whole manuscript, no mention was done with regards to the presence of studies dealing specifically with Heart failure with preserved ejection fraction. It seems that all studies dwelled upon heart failure with reduced ejection fraction. If this is the case, I would change the title into "Effectiveness of implementation interventions in improving physician adherence to guideline recommendations in heart failure with reduced ejection fraction: a systematic review". Moreover the definition heart failure with reduced ejection fraction (HFrEF) should also be used in the manuscript instead of the generic all-encompassing heart failure.

RESPONSE: [While we did not limit our search to studies on patients with HFrEF, majority of the included studies were focused on this patient population. This is because, at present, the American Heart Association only offers Class I recommendations on pharmacological and device therapies for patients with HFrEF. However, Class I recommendations regarding patient education and LVEF assessment are generalized to all HF patients, and studies that reported these process outcomes were not always limited to patients with HFrEF.

We have added the definition for HFrEF and HFpEF into the introduction, along with a note that Class I recommendations on pharmacological and device therapies are currently only available for patients with HFrEF.(pages 3,4; Introduction paragraph 1)]

-Abstract: The results section of the abstract is quite long and hard to follow. I would suggest to delate the description of the type of study "including 9 randomized controlled trials (RCTs). Provider level interventions (N=13 studies) included: audit and feedback, reminders, and education. Organization-level interventions (N=15) included: medical records systems changes, multidisciplinary teams, and clinical pathways. System-level interventions (N=3) included: provider/institutional incentives. Four studies assessed multi-level interventions."

RESPONSE: [We have deleted "9 randomized controlled trials (RCTs)" from the abstract. However, we feel it is valuable, to readers, to present a list of all the interventions studied, and how they are categorized within the different levels.(Page 2)]

-Abstract: I would add in the conclusion (page 3 lines 14) "However, improvements in process outcomes were rarely accompanied by improvements in clinical outcomes. "

RESPONSE: [We have added this statement to the conclusion section of the abstract.(page 3)]

-Results: there were studies dealing with the target dose for each kind of medications? How many patients reached the target dose of ACE-I or Beta-blockers or MRA after implementation of interveniuon.

RESPONSE: [The proportion of patients reaching target dose of specific medications as a result of an implementation intervention are detailed in the paragraphs 1 and 2 of the results subsection titled "Prescription of target-dose medications".(pages 30,31)]

-The discussion is too long and very hard to follow. Moreover I would be more focused on these aspects: 1) conclusion cannot be drawn from this work 2) which kind of guidelines measures were the most studied (acei? Betablockers? ICD?) 3) the authors should also discuss the importance of reaching the target dose for medications.

RESPONSE: [We have added to the discussion the number of studies reporting prescription of specific medication types (Page 34, Discussion paragraph 2) and also a note on why implementation interventions that improve target-dose prescription are important (Page 35, Discussion paragraph 3). We have also made an effort to present the existing discussion more succinctly, and emphasized that conclusions cannot be drawn from the work.]

Reviewer: 3

Reviewer Name: Ulrich Siering

Institution and Country: Institute for Quality and Efficiency in Health Care (IQWiG)

Department for Health Care and Health Economics, Germany

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

Page 4. line 18: There are several more current systematic reviews on guideline implementation. The review of Grimshaw contains only studies published until 1998.

More current reviews are listed here (from page 158ff): https://www.iqwig.de/download/V12-04_Abschlussbericht_Umsetzung-von-Leitlinien.pdf

Perhaps also interesting:

Unverzagt S, Oemler M, Braun K, Klement A. Strategies for guideline implementation in primary care focusing on patients with cardiovascular disease: a systematic review. Fam Pract 2014; 31(3): 247-266

RESPONSE: [We have cited reviews by Unverzagt et al. and Brusamento et al. as references 11 and 12.(page 42)]

Page 11ff, Table 3: The control interventions should be mentioned - in table 3 and the corresponding text.

RESPONSE: [In most cases, the control was usual care with no implementation intervention. We have added this and described details of control interventions, when used, in Table 3.(pages 11-26)]

Page 25, table 4: Table 4 is not helpful. It should be considered to delete the table or to find a different form of presentation.

RESPONSE: [We have deleted Table 4.]

Page 34. line 49 and page 35. line 35: Citation [58] and [60] are the same

RESPONSE: [We have deleted the duplicate reference.]

Page 35. line 16. The statement that audit and feedback are "largely ineffective" is not correct. Die Conclusion of Ivers et al is: "AUTHORS' CONCLUSIONS: Audit and feedback generally leads to small but potentially important improvements in professional practice. The effectiveness of audit and

feedback seems to depend on baseline performance and how the feedback is provided. Future studies of audit and feedback should directly compare different ways of providing feedback." Ivers et al should be cited correctly.

RESPONSE: [We have edited the statement, and corrected the citation of the paper by Ivers et al (Pages 34,35; Discussion paragraph 2):

"However, on the whole, the results across a number of studies suggest that educational seminars,[30] and audit and feedback [20,21] are minimally effective in isolation. Audit and feedback appears to be an important component of multifaceted interventions, however, [34,55,57,58] and it is possible that factors such as the type of feedback and co-interventions to address gaps in care can influence its effectiveness.[61]"

Page 35, line 27: Citation [64] is the updated version of [65]. I think, it is not necessary to cite [65].

RESPONSE: [We have deleted citation 65.]

Page 36, line 21ff: The authors state, that one of the greatest limitation of their study is the inclusion of studies with "observational and quasi-experimental study design". The authors should explain, why the inclusion of these studies was necessary.

RESPONSE: [Paragraph 10 of the discussion offers an explanation as to the challenges of conducting controlled trials in implementation research, and why observational and quasi-experimental designs are deemed to be more feasible. As such, excluding observational and quasi-experimental study design would have reduced the scope of our review.(pages 37,38)]

Page 51. fig. 1: The numbers in the flow chart are not correct: Article Screened: 2424, excluded: 2299, Full-text: 126. 2299+126 = 2425 (not: 2424)

RESPONSE: [These numbers have been corrected and updated to include the results from the more recent search.(page 10, Results subsection "Identification, screening, and selection of studies")]

We are resubmitting the revised manuscript and trust that you will find it worthy of publication.

VERSION 2 – REVIEW

REVIEWER	Pierpaolo Pellicori Academic Cardiology, Hull and York Medical School, UK
REVIEW RETURNED	21-Dec-2017

GENERAL COMMENTS	I am satisfied with authors' reply.
-------------------------	-------------------------------------

REVIEWER	Antonio Cittadini Professor of Internal Medicine University Federico II 80131 Naples ITALY email: antonio.cittadini@unina.it Tel-Fax: +39 81 7464375
-----------------	---

	Head of Interdisciplinary Research Centre in Biomedical Materials (C.R.I.B.) Piazzale Tecchio, 80 80125 Naples, ITALY
REVIEW RETURNED	18-Dec-2017

GENERAL COMMENTS	I am satisfied by the answer of the authors. I don't have any further request.
-------------------------	--

REVIEWER	Ulrich Siering Institute for Quality and Efficiency in Health Care (IQWiG) Germany I am author of the publication "1. Siering U, Eikermann M, Hausner E, Hoffmann-Esser W, Neugebauer EA. Appraisal tools for clinical practice guidelines: a systematic review. PLoS One 2013; 8(12): e82915."
REVIEW RETURNED	15-Dec-2017

GENERAL COMMENTS	Thank you for the Revision of the article
-------------------------	---